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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,191	09/23/2005	Shinji Iijima	12218/46	6125

23838 7590 09/18/2007

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ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
09/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/523,191	IIJIMA ET AL.	
	Examiner	Art Unit	
	Kevin K. Hill, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 January 2005* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Claims 1-59 are under consideration.

Priority

This application is a 371 of PCT/JP03/10198, filed August 11, 2003. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Acknowledgment is also made of Applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d).

While a certified copy of JP 2002-236089, filed August 13, 2002, and PCT/JP03/10198, filed August 11, 2003 have been filed with the instant application, certified English translations of the priority documents have not been provided.

The Examiner is unable to find support in the instant specification for a selection method recited in claim 57 comprising confirming a transgene in the sperm of a male G0 transgenic bird. Accordingly, the effective priority date of the instant application is granted as the filing date of the instant application, September 23, 2005.

If applicant believes the earlier applications provide support for this disclosure, applicant should point out such support by page and line number in the reply to this Action.

Information Disclosure Statement

Applicant has filed Information Disclosure Statements on April 25, 2005, May 26, 2006 and August 9, 2006 that have been considered. The signed and initialed PTO Forms 1449 are mailed with this action.

Drawings

New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because the drawing legends comprise misspellings in the figure legends, e.g. "incubatuion" in Figures 2-3 and "conentration" in Figures 8-11. Applicant is advised to employ

the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Claim Objections

1. **Claims 8 and 33 are objected to because of the following informalities:** the claims embrace a transgenic bird comprising retrovirus vector having a VSV-G protein-containing membrane. However, the claims are objected to since VSV-G protein is normally associated with the retroviral envelope, not the inventive nucleic acid vector comprising the inventive transgene that will integrate into the genome of the transgenic bird does not comprise membranes nor the gene coding for VSV-G. Rather, a helper virus that will not be a structural element of the transgenic bird is used to express virion packaging and supplemental membrane proteins, conferring the VSV-G pseudotype. Thus, the VSV-G pseudotype confers no heritable structural feature onto the transgenic bird.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2.. **Claims 42-45 and 48 are rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With respect to claims 42-45, where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one

reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The term "mating type allogeanic" is indefinite because the specification does not clearly define the term.

Furthermore, claims 42-43 recite the G0 transgenic chimera bird of claim 42 is to be mated with...the mating type allogeanic bird is the G0 transgenic bird (claim 43). The Examiner notes that there is no disclosure in the specification demonstrating that the inventive transgenic chimera bird can self-mate and self-fertilize, that is to say, becomes hermaphroditic as a consequence of the method of transgenesis.

With respect to claim 48, the claim recites the phrase "the transgenic bird" in reference to claim 42. However, claim 42 recites a plurality of transgenic birds, and thus it is unclear to which transgenic bird claim 48 refers.

Correction and/or clarification is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. **Claim 57 is rejected under 35 U.S.C. 102(b)** as being anticipated by Harvey et al (2002; *of record in IDS).

Harvey et al teach a method of selecting germline transgenic chimera birds comprising the step of confirming a transgene in the sperm of a male G0 transgenic bird (pg 204, Sperm DNA Extraction; pg 206, Table 1).

4. **Claims 1, 5, 8-9, 24, 41-57 are rejected under 35 U.S.C. 102(e)** as being anticipated by Ivarie et al (U.S. Patent No. 6,730,822).

Ivarie et al disclose a method of making transgenic birds, e.g. chicken and turkeys (col. 7, line 26) so as to express exogenous proteins, wherein the exogenous genes can be transmitted to the bird's offspring stably in a Mendelian fashion (col. 5, lines 1-5). Absent evidence to the contrary, one of ordinary skill in the art would reasonably interpret transmission to a bird's offspring stably in a Mendelian fashion to reasonably embrace subsequent matings of the transgenic bird to maintain the transgenic stock. Ivarie et al disclose the transduction of blastodermal cells to generate the transgenic birds (col. 18, lines 56-65), wherein the resulting chimeric chick (founder) is grown to maturity. Because some founders are germline founders, offspring can be tested for expression of the exogenous gene in a specific tissue of the bird (col. 19, lines 1-23). Ivarie et al disclose the generation of White Leghorn transgenic chimera chickens (col. 20, Example 3), wherein the transgenic male chickens were mated to White Leghorn female chickens that are allogeanic, absent evidence to the contrary (col. 26, lines 17-27). Ivarie et al also disclose a method of selecting germline transgenic birds comprising confirming a transgene in the sperm of a male G0 transgenic birds (col.s 25-26, Example 10). Ivarie et al do not teach the White Leghorn strain to be "mating type allogeanic". However, absent a definition of the term, the Examiner has used the term "allogenic", which the art recognizes to mean "Being genetically different although belonging to or obtained from the same species." (www.thefreedictionary.com/allogeneic, last visited September 5, 2007). Thus, the non-transgenic White Leghorn chickens mated to the transgenic White Leghorn chickens are considered to be allogenic for being of the same species, and more particularly, the same strain.

Ivarie et al disclose the use of replication-defective pNLB vectors derived from an avian leukosis retroviral vector (col. 7, lines 60-62; col. 11, lines 17-20; col. 13, lines 30-35) comprising constitutive promoters, e.g. a β-actin promoter (col. 6, lines 39-41), or tissue-specific promoters, e.g. an ovalbumin promoter (col. 7, line 47; col. 12, lines 5-9). The transgenic birds

for the purposes of the instant rejection are merely required to comprise a replication-defective retroviral vector. It is noted that the retroviral vector does not comprise a gene coding for VSV-G. The VSV-G protein is necessary for entry into cells, but is not present in the transgenic birds or their offspring. Therefore, any transgenic bird in the prior art comprising a replication-defective retroviral vector would anticipate claims having limitations embracing VSV-G.

Ivarie et al contemplate the exogenous protein expressed by the transgenic bird may be, for example, a genetically engineered antibody (col. 19, lines 25-42), wherein the exogenous antibody derived from the transgene may be expressed in at least one of blood, albumen, and egg yolk, Ivarie et al disclose the exogenous protein may be deposited into the blood, albumen or egg yolk (col. 4, line 67; col. 12, line 5; col. 15, line 12). Ivarie et al contemplate an egg laid by a G1 transgenic bird may contain up to 1.75μg/ml (assuming 40mL of egg white per egg) or 20-40mg/egg of the heterogeneous protein encoded by the transgene (col. 22, Table 1, lines 19-21; col. 23, lines 14-16). Ivarie et al do not disclose the amounts instantly recited in claims 51-56; however, absent evidence to the contrary, the instantly recited amounts of recombinant antibody to be present in the blood, albumen or egg yolk are inherent features obtained by the structural elements of the retroviral vector used to make the transgenic bird. Thus, the transgenic birds of Ivarie et al would inherently possess such amounts of recombinant antibody in the blood, albumen or yolk because the instantly claimed structural elements of the retroviral vector are indistinguishable from Ivarie et al.

With respect to claims 41, 44-45, 47 and 53-54, the G0 transgenic chimera bird, and G1 and G2 transgenic bird, and transgenic eggs laid by said transgenic birds as claimed are determined to be a product-by-process claims. The structural elements of the transgenic bird, specifically that it possesses a retroviral vector encoding an exogenous transgene are fulfilled. The recitation of a process limitation in claims 41, 44-45 and 47 are not viewed as positively limiting the claimed product absent a showing that the process of making recited in claim 25 imparts a novel or unexpected property to the claimed transgenic bird product, as it is assumed that equivalent transgenic bird products are obtainable by multiple routes. The recitation "obtainable by" is not considered to limit the claimed transgenic bird because the G1 and G2 transgenic birds may be obtained by other reproductive means. The burden is placed upon the

applicants to establish a patentable distinction between the claimed and referenced products. The method in which the transgenic birds were produced is immaterial to their patentability.

"Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP §2113.

5. **Claims 1, 5, 7-16, 24, 41, 44-56 and 58-59 are rejected under 35 U.S.C. 102(e)** as being anticipated by Rapp et al (US2002/0108132 A1).

With respect to the limitation of a transgenic bird comprising a transgene that encodes an exogenous polypeptide that is an antibody, Rapp et al contemplate transgenic chickens and quails (pg 4, [0041]) transformed with recombinant retroviral expression vectors, including a Moloney murine leukemia virus-derived vector (pg 5, [0052, 0054]; pg 9, [0094-0095]; pg 16, [0158]), wherein said vectors comprise a gene encoding [chimeric] antibodies comprising human immunoglobulin constant domains, single-chain antibodies, and antibody fragments and/or from birds or mice (pgs 6-7, [0062-0068]; pg 15, [0151]; pg 16, [0161]) operably linked to, for example, constitutive promoters (pg 9, [0090]; pg 16, [0159]). It is noted that the retroviral vector does not comprise a gene coding for VSV-G. The VSV-G protein is necessary for entry into cells, but is not present in the transgenic birds or their offspring. Therefore, any transgenic bird in the prior art comprising a replication-defective retroviral vector would anticipate claims having limitations embracing VSV-G.

With respect to the limitation that the antibody be expressed in the blood, albumen and/or egg yolk, Rapp et al disclose that the recombinant antibodies may be obtained from the blood or egg tissues (pg 11, [0108]; pg 16, [0163], [0166]). Absent evidence to the contrary, the recited amounts of recombinant antibody to be present in the blood, albumen or egg yolk are inherent features obtained by the structural elements of the retroviral vector used to make the transgenic bird. Thus, the transgenic birds of Rapp et al would inherently possess such amounts of

recombinant antibody in the blood, albumen or yolk because the instantly claimed structural elements of the retroviral vector are indistinguishable from Rapp et al.

With respect to the limitations regarding the quantity of heterologous antibody present in the eggs laid by the transgenic birds, (claims 49-56), absent evidence to the contrary, the recited amounts of recombinant antibody to be present in the blood, albumen or egg yolk are inherent features obtained by the structural elements of the retroviral vector used to make the transgenic bird. Thus, the transgenic birds of Rapp et al would inherently possess such amounts of recombinant antibody in the blood, albumen or yolk because the instantly claimed structural elements of the retroviral vector are indistinguishable from Rapp et al.

With respect to claims 41, 44-47 and 53-56, the G0 transgenic chimera bird, and G1 and G2 transgenic bird, and transgenic eggs laid by said transgenic birds as claimed are determined to be a product-by-process claims. The structural elements of the transgenic bird, specifically that it possesses a retroviral vector encoding an exogenous transgene are fulfilled. The recitation of a process limitation in claims 41, 44-45 and 47 are not viewed as positively limiting the claimed product absent a showing that the process of making recited in claim 25 imparts a novel or unexpected property to the claimed transgenic bird product, as it is assumed that equivalent transgenic bird products are obtainable by multiple routes. The burden is placed upon the applicants to establish a patentable distinction between the claimed and referenced products. The method in which the transgenic birds were produced is immaterial to their patentability. The transgenic animal can, in turn, be bred by natural mating (pg 14, [0143]). The recitation "obtainable by" is not considered to limit the claimed transgenic bird because the G1 and G2 transgenic birds may be obtained by other reproductive means. Absent evidence to the contrary, the steps of breeding a transgenic bird are separate and distinct from the steps of making a transgenic bird because the transgene has already integrated into the genome and there is no limitation that clearly distinguishes the mating of transgenic birds from non-transgenic birds.

"Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior

product was made by a different process." *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP §2113.

With respect to the selection method, Rapp et al disclose a method of selecting transgenic birds comprising the step of detecting the expression of the heterologous polypeptide in the blood (pg 19, [0191]).

6. **Claims 1-5, 7-16, 24 and 41-59 are rejected under 35 U.S.C. 102(e)** as being anticipated by Rapp et al (US2003/0126629), as evidenced by Kines et al (Exp. Parasitol. 112(4): 209-220, 2006; Abstract only).

With respect to the limitation of a transgenic bird comprising a transgene that encodes an exogenous polypeptide that is an antibody, Rapp et al disclose a genus of recombinant antibody constructions comprising immunoglobulin heavy chains, light chains, constant regions, variable regions, single-chain antibodies, wherein said antibodies may be chimeric and from different animal species, including humans, mouse and chicken (pg 4, [0032]; pg 7, [0061-0062]; pgs 25-26, [0258, 0263-0271]).

With respect to the limitation that the antibody gene is controlled by a constitutive promoter, Rapp et al disclose the use of non-tissue specific promoters such as CMV or RSV (pg 26, [0267]).

With respect to the limitation that the antibody be expressed in the blood, albumen and/or egg yolk, Rapp et al disclose that the recombinant antibodies may be obtained from the blood or egg tissues (pg 26, [0270]). Absent evidence to the contrary, the recited amounts of recombinant antibody to be present in the blood, albumen or egg yolk are inherent features obtained by the structural elements of the retroviral vector used to make the transgenic bird. Thus, the transgenic birds of Rapp et al would inherently possess such amounts of recombinant antibody in the blood, albumen or yolk because the instantly claimed structural elements of the retroviral vector are indistinguishable from Rapp et al. Rapp et al disclose the amount of recombinant antibody to be present in the blood, albumen or egg yolk (pg 3, [0030]; pg 20, [0206]).

With respect to the limitations that the retrovirus vector is derived from Moloney murine leukemia virus (MuLV) or a vector that is a VSV-G pseudotype, Rapp et al disclose the preparation of a Murine Leukemia virus, VSV-G pseudotype stock, wherein the recombinant

retroviral vector pLNHX is recognized in the art as being derived from a Moloney murine leukemia virus (Kines et al). It is noted that the retroviral vector does not comprise a gene coding for VSV-G. The VSV-G protein is necessary for entry into cells, but is not present in the transgenic birds or their offspring. Therefore, any transgenic bird in the prior art comprising a replication-defective retroviral vector would anticipate claims having limitations embracing VSV-G.

With respect to the limitation of a transgenic bird, Rapp et al contemplate transgenic chickens and quails (pg 4, [0039]).

With respect to claims 41-47 and 53-56, the G0 transgenic chimera bird, and G1 and G2 transgenic bird, and transgenic eggs laid by said transgenic birds as claimed are determined to be a product-by-process claims. The structural elements of the transgenic bird, specifically that it possesses a retroviral vector encoding an exogenous transgene are fulfilled. The recitation of a process limitation in claims 41, 44-45 and 47 are not viewed as positively limiting the claimed product absent a showing that the process of making recited in claim 25 imparts a novel or unexpected property to the claimed transgenic bird product, as it is assumed that equivalent transgenic bird products are obtainable by multiple routes. The burden is placed upon the applicants to establish a patentable distinction between the claimed and referenced products. The method in which the transgenic birds were produced is immaterial to their patentability. The recitation "obtainable by" is not considered to limit the claimed transgenic bird because the G1 and G2 transgenic birds may be obtained by other reproductive means. Rapp et al contemplate the creation of transgenic White Leghorn chickens, as well as the breeding to allogeanic birds and maintenance of transgenic avians (pg 17, [0177-0180]; pg 33, [0330]; pg 35, [0347]). Absent evidence to the contrary, the steps of breeding a transgenic bird are separate and distinct from the steps of making a transgenic bird because the transgene has already integrated into the genome and there is no limitation that clearly distinguishes the mating of transgenic birds from non-transgenic birds.

"Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior

product was made by a different process." *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP §2113.

With respect to the selection methods, Rapp et al disclose detecting the presence of the transgene either by DNA of the sperm and/or detection of protein in the blood (pg 10, [0107]; pg 30, Table 1; pg 33, [0330]).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. **Claims 1, 5, 7-16, 24, 41-59 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Ivarie et al (U.S. Patent No. 6,730,822) and Rapp et al (US2002/0108132 A1).

Ivarie et al disclose a method of making transgenic birds, e.g. chicken and turkeys (col. 7, line 26) so as to express exogenous proteins, wherein the exogenous genes can be transmitted to the bird's offspring stably in a Mendelian fashion (col. 5, lines 1-5). Ivarie et al disclose the transduction of blastodermal cells to generate the transgenic birds (col. 18, lines 56-65), wherein

the resulting chimeric chick (founder) is grown to maturity. Because some founders are germline founders, offspring can be tested for expression of the exogenous gene in a specific tissue of the bird (col. 19, lines 1-23). Ivarie et al disclose the generation of White Leghorn transgenic chimera chickens (col. 20, Example 3), wherein the transgenic male chickens were mated to White Leghorn female chickens that are allogenic, absent evidence to the contrary (col. 26, lines 17-27). Ivarie et al also disclose a method of selecting germline transgenic birds comprising confirming a transgene in the sperm of a male G0 transgenic birds (col.s 25-26, Example 10). Ivarie et al do not teach the White Leghorn strain to be "mating type allogeanic". However, absent a definition of the term, the Examiner has used the term "allogenic", which the art recognizes to mean "Being genetically different although belonging to or obtained from the same species." (www.thefreedictionary.com/allogeneic, last visited September 5, 2007). Thus, the non-transgenic White Leghorn chickens mated to the transgenic White Leghorn chickens are considered to be allogenic for being of the same species, and more particularly, the same strain.

Ivarie et al disclose the use of replication-defective pNLB vectors derived from an avian leukosis retroviral vector (col. 7, lines 60-62; col. 11, lines 17-20; col. 13, lines 30-35) comprising constitutive promoters, e.g. a β-actin promoter (col. 6, lines 39-41), or tissue-specific promoters, e.g. an ovalbumin promoter (col. 7, line 47; col. 12, lines 5-9). The transgenic birds for the purposes of the instant rejection are merely required to comprise a replication-defective retroviral vector. It is noted that the retroviral vector does not comprise a gene coding for VSV-G. The VSV-G protein is necessary for entry into cells, but is not present in the transgenic birds or their offspring. Therefore, any transgenic bird in the prior art comprising a replication-defective retroviral vector would anticipate claims having limitations embracing VSV-G.

Ivarie et al contemplate the exogenous protein expressed by the transgenic bird may be, for example, a genetically engineered antibody (col. 19, lines 25-42), wherein the exogenous antibody derived from the transgene may be expressed in at least one of blood, albumen, and egg yolk, Ivarie et al disclose the exogenous protein may be deposited into the blood, albumen or egg yolk (col. 4, line 67; col. 12, line 5; col. 15, line 12). Ivarie et al contemplate an egg laid by a G1 transgenic bird may contain up to 1.75μg/ml (assuming 40mL of egg white per egg) or 20-40mg/egg of the heterogeneous protein encoded by the transgene (col. 22, Table 1, lines 19-21; col. 23, lines 14-16). Ivarie et al do not disclose the amounts instantly recited in claims 51-56;

however, absent evidence to the contrary, the instantly recited amounts of recombinant antibody to be present in the blood, albumen or egg yolk are inherent features obtained by the structural elements of the retroviral vector used to make the transgenic bird. Thus, the transgenic birds of Ivarie et al would inherently possess such amounts of recombinant antibody in the blood, albumen or yolk because the instantly claimed structural elements of the retroviral vector are indistinguishable from Ivarie et al.

The G0 transgenic chimera bird, and G1 and G2 transgenic bird, and transgenic eggs laid by said transgenic birds as claimed are determined to be a product-by-process claims. The structural elements of the transgenic bird, specifically that it possesses a retroviral vector encoding an exogenous transgene are fulfilled. The recitation of a process limitation in claims 41, 44-45 and 47 are not viewed as positively limiting the claimed product absent a showing that the process of making recited in claim 25 imparts a novel or unexpected property to the claimed transgenic bird product, as it is assumed that equivalent transgenic bird products are obtainable by multiple routes. The recitation "obtainable by" is not considered to limit the claimed transgenic bird because the G1 and G2 transgenic birds may be obtained by other reproductive means. The burden is placed upon the applicants to establish a patentable distinction between the claimed and referenced products. The method in which the transgenic birds were produced is immaterial to their patentability.

"Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP §2113.

Ivarie et al do not teach the transgene encodes a chimeric antibody (claims 10-16), nor a selection method comprising confirming a transgene-derived protein expression in the blood (claims 58-59). However, at the time of the invention, Rapp et al disclosed a transgenic bird comprising a transgene that encodes an exogenous polypeptide that is an antibody, Rapp et al contemplate transgenic chickens and quails (pg 4, [0041]) transformed with recombinant

retroviral expression vectors, including a Moloney murine leukemia virus-derived vector (pg 5, [0052, 0054]; pg 9, [0094-0095]; pg 16, [0158]), wherein said vectors comprise a gene encoding [chimeric] antibodies comprising human immunoglobulin constant domains, single-chain antibodies, and antibody fragments and/or from birds or mice (pgs 6-7, [0062-0068]; pg 15, [0151]; pg 16, [0161]) operably linked to, for example, constitutive promoters (pg 9, [0090]; pg 16, [0159]). It is noted that the retroviral vector does not comprise a gene coding for VSV-G. The VSV-G protein is necessary for entry into cells, but is not present in the transgenic birds or their offspring. Therefore, any transgenic bird in the prior art comprising a replication-defective retroviral vector would anticipate claims having limitations embracing VSV-G.

Rapp et al disclose that the recombinant antibodies may be obtained from the blood or egg tissues (pg 11, [0108]; pg 16, [0163], [0166]). Absent evidence to the contrary, the recited amounts of recombinant antibody to be present in the blood, albumen or egg yolk are inherent features obtained by the structural elements of the retroviral vector used to make the transgenic bird. Thus, the transgenic birds of Rapp et al would inherently possess such amounts of recombinant antibody in the blood, albumen or yolk because the instantly claimed structural elements of the retroviral vector are indistinguishable from Rapp et al.

With respect to the limitations regarding the quantity of heterologous antibody present in the eggs laid by the transgenic birds, absent evidence to the contrary, the recited amounts of recombinant antibody to be present in the blood, albumen or egg yolk are inherent features obtained by the structural elements of the retroviral vector used to make the transgenic bird. Thus, the transgenic birds of Rapp et al would inherently possess such amounts of recombinant antibody in the blood, albumen or yolk because the instantly claimed structural elements of the retroviral vector are indistinguishable from Rapp et al.

The G0 transgenic chimera bird, and G1 and G2 transgenic bird, and transgenic eggs laid by said transgenic birds as claimed are determined to be a product-by-process claims. The structural elements of the transgenic bird, specifically that it possesses a retroviral vector encoding an exogenous transgene are fulfilled. The recitation of a process limitation in claims 41, 44-45 and 47 are not viewed as positively limiting the claimed product absent a showing that the process of making recited in claim 25 imparts a novel or unexpected property to the claimed transgenic bird product, as it is assumed that equivalent transgenic bird products are obtainable

by multiple routes. The burden is placed upon the applicants to establish a patentable distinction between the claimed and referenced products. The method in which the transgenic birds were produced is immaterial to their patentability. The transgenic animal can, in turn, be bred by natural mating (pg 14, [0143]). The recitation "obtainable by" is not considered to limit the claimed transgenic bird because the G1 and G2 transgenic birds may be obtained by other reproductive means. Absent evidence to the contrary, the steps of breeding a transgenic bird are separate and distinct from the steps of making a transgenic bird because the transgene has already integrated into the genome and there is no limitation that clearly distinguishes the mating of transgenic birds from non-transgenic birds.

"Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP §2113.

Rapp et al disclose a method of selecting transgenic birds comprising the step of detecting the expression of the heterologous polypeptide in the blood (pg 19, [0191]).

It would have been obvious to one of ordinary skill in the art to substitute the antibody gene of Ivarie et al with the antibody gene of Rapp et al with a reasonable chance of success because the simple substitution of one known, equivalent element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

It also would have been obvious to one of ordinary skill in the art to combine and/or substitute the selection method of Rapp et al with the selection method of Ivari et al with a reasonable chance of success because the particular known techniques of selecting transgenic organisms either by nucleic acid methods using tissue samples from sperm and/or blood or by methods of detecting protein from blood sera were well-known in the art, and thus was recognized as part of the ordinary capabilities of one skilled in the art.

It also would have been obvious to one of ordinary skill in the art to mate the G0 transgenic bird to a G0 offspring thereof because the art has long-recognized the necessity of

mating two heterozygous animals to achieve a homozygous animal. In the instant case, a heterozygous transgenic bird must be mated with another heterozygous, transgenic bird of the identical transgenic event so as to create a homozygous, transgenic bird, assuming said homozygote is viable.

Thus, the invention as a whole is *prima facie* obvious.

8. **Claims 1-4 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Ivarie et al (U.S. Patent No. 6,730,822) and Rapp et al (US2002/0108132 A1), as applied to claims 1, 5, 7-16, 24, 41-59 above, and in further view of Chad et al (Curr. Op. Biotechnology 12(2): 188-194, 2001).

Ivarie et al and Rapp et al do not teach the antibody constant region is IgG or IgG1; however, at the time of the invention, Chad et al taught that any different antibody structures have been generated using standard expression technology. These include full-length antibodies, antibody fragments (Fab or [Fab']2), and scFv (pgs 188 189, joining sentence). If pharmacokinetic activity in the form of increased half-life is required for therapeutic purposes, however, then a full-length antibody is preferred. For immunoglobulin G (IgG), the molecule can be one of four subclasses: γ1, γ2, γ3 or γ4. If a full-length antibody with effector function is needed, a γ1 subclass is preferred (pg 189, col. 1).

It would have been obvious to one of ordinary skill in the art to substitute the antibody constant domain of Ivarie et al or Rapp et al with an IgG or IgG1 domain as taught by Chad et al with a reasonable chance of success because the simple substitution of one known, equivalent element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Thus, the invention as a whole is *prima facie* obvious.

9. **Claims 1 and 6 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Ivarie et al (U.S. Patent No. 6,730,822) and Rapp et al (US2002/0108132 A1), Chad et al (Curr. Op. Biotechnology 12(2): 188-194, 2001), as applied to claims 1-5, 7-16, 24, 41-59 above, and in further view of Guild et al (J. Virology 62(10): 3795-3801, 1988).

The prior cited art does not teach the use of the specific chicken β-actin promoter; however, at the time of the invention, Guild et al taught the use of the chicken β-actin promoter in a recombinant Moloney murine leukemia virus vector (pg 3796, col. 2, Construction of internal promoter vectors).

It would have been obvious to one of ordinary skill in the art to substitute the constitutive promoter taught by Rapp et al, and in particular the β-actin promoter taught by Ivarie et al, with the chicken β-actin promoter as taught by Guild et al with a reasonable chance of success because the art has long-recognized the ability to use the chicken β-actin promoter with recombinant viral vectors and the simple substitution of one β-actin promoter for a known, equivalent β-actin promoter would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Thus, the invention as a whole is *prima facie* obvious.

10. **Claims 1 and 17-23 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Ivarie et al (U.S. Patent No. 6,730,822) and Rapp et al (US2002/0108132 A1), Chad et al (Curr. Op. Biotechnology 12(2): 188-194, 2001) and Guild et al (J. Virology 62(10): 3795-3801, 1988), as applied to claims 1-16, 24, 41-59 above, and in further view of Powers et al (J. Immunol. Methods 251: 123-135, 2001; *of record in IDS), as evidenced by Ono et al (J. Biosci. And Bioeng. 95(3): 231-238, 2003).

The prior cited art does not teach the antibody gene to encode a single-chain Fv-Fc fusion; however, at the time of the invention, Powers et al taught the construction of a single-chain Fc-Fv fusion gene expressed heterologously in yeast.

It would have been obvious to one of ordinary skill in the art to substitute the antibody gene of Ivarie et al or Rapp et al with the antibody gene of Powers et al with a reasonable chance of success because the simple substitution of one known, equivalent element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

An artisan would have been motivated to express an scFc-Fv fusion gene in chickens because Chad et al teach that unlike bacterial expression, animal cell culture and transgenic animal systems have the greatest potential to produce oligosaccharides similar to those contained in human antibodies (Chad et al, pg 189, col.s 1-2, joining sentence). Both human and chicken

antibodies can contain oligosaccharides with only the sialic acid *N*-acetylneuraminic acid (NANA), whereas all other species can produce antibodies containing only the sialic acid *N*-glycosylneuraminic acid (NGNA) or a mixture of NGNA and NANA (pg 189, col. 2). The transgenic production of antibodies in egg white has the potential to supply large quantities of material for clinical trials relatively inexpensively. For example, a flock of 5000 chickens is estimated to produce 125kg of unpurified antibody/year (100 mg antibody/egg and 250 eggs/chicken/year). The commercial cost of chicken eggs (produced under conditions that do not comply with current good manufacturing practice [cGMP]) is currently $0.05/egg. Hence, the cost of generating unpurified material from transgenic chickens is calculated at $0.5/g (Chad et al, pg 191, col. 2, Chickens).

Transgenic production can achieve a lower cost of goods for large-scale manufacturing. Recent advances in the expression of antibodies in transgenic goats, chickens and plants—with respect to productivity, competitive timelines and cost of goods—suggest the need to seriously evaluate these recombinant systems as alternative platforms. Comparing cost of goods analyses between cell culture and the various transgenic production systems, expression in transgenic chickens appears to show great promise when compared with goats and plants (Chad et al, pg 192, col. 2, Conclusions). See also Ono et al for working examples in the art teaching a recombinant retrovirus encoding an scFv-Fc antibody fusion in chicken cells.

Thus, the invention as a whole is *prima facie* obvious.

11. **Claims 25-29, 34-35, 37 and 42-43 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Mizuarai et al (J. Biochem. (January) 129: 125-132, 2001) and Ivarie et al (U.S. Patent No. 6,730,822), as evidenced by Perry et al (Transgenic Res. 2: 125-133, 1993).

Mizuarai et al (2001) teach a method of making transgenic quail comprising the use of a replication-defective retroviral vector encoding β-galactosidase under the control of a chicken β-actin and Rous sarcoma virus hybrid promoter (pg 126, col. 1, Recombinant Plasmids), wherein a composition comprising said vector was introduced into the heart of a 48-hour stage embryo (pg 127, col. 2, lines 1-5), the method comprising incubation of said eggs (pg 127, col. 2).

Mizuarai et al do not teach the hatching of the embryos; however, at the time of the invention, Ivarie et al disclosed a method of making transgenic birds, e.g. chickens (col. 7, line

26) so as to express exogenous proteins, wherein the exogenous genes can be transmitted to the bird's offspring stably in a Mendelian fashion (col. 5, lines 1-5). Ivarie et al disclose the use of replication-defective pNLB vectors derived from an avian leukosis retroviral vector (col. 7, lines 60-62; col. 11, lines 17-20; col. 13, lines 30-35) comprising constitutive promoters, e.g. a β-actin promoter (col. 6, lines 39-41). Ivarie et al contemplate the retroviral vector to encode an exogenous protein that may be, for example, a genetically engineered antibody (col. 19, lines 25-42). Ivarie et al disclose the infection of blastodermal cells with at least 10^7 virus particles to generate the transgenic birds (col. 18, lines 56-65; col. 20, Examples 2-3), wherein the resulting chimeric chick (founder) is grown to maturity. Because some founders are germline founders, offspring can be tested for expression of the exogenous gene in a specific tissue of the bird (col. 19, lines 1-23). Ivarie et al disclose the generation of White Leghorn transgenic chimera chickens (col. 20, Example 3), wherein the transgenic male chickens were mated to White Leghorn female chickens that are allogenic, absent evidence to the contrary (col. 26, lines 17-27). Ivarie et al also disclose a method of selecting germline transgenic birds comprising confirming a transgene in the sperm of a male G0 transgenic birds (col.s 25-26, Example 10). Ivarie et al do not teach the White Leghorn strain to be "mating type allogeanic". However, absent a definition of the term, the Examiner has used the term "allogenic", which the art recognizes to mean "Being genetically different although belonging to or obtained from the same species." (www.thefreedictionary.com/allogeneic, last visited September 5, 2007). Thus, the non-transgenic White Leghorn chickens mated to the transgenic White Leghorn chickens are considered to be allogenic for being of the same species, and more particularly, the same strain.

It would have been obvious to one of ordinary skill in the art to modify the method of Mizuarai et al to introduce virus particles comprising replication-defective retroviral vector as taught by Ivarie et al rather than replication-defective retroviral vector nucleic acid into the heart of a 48-hour stage embryo with a reasonable chance of success because the art has long recognized the ability to infect chicken embryos with replication-defective retroviruses, and that primordial germ cells migrate in the vascular blood system and colonize the germinal ridges around the end of Day 4 of development (Perry et al, pg 126, col. 2, ¶1). Intravascular microinjection would expose migrating primordial germ cells to the virus for infection. An artisan would be motivated to introduce virus particles because Mizuarai et al teach the addition

of protamine-modified lipid vesicles to pantropic retroviral particles increased the viral titer (10^8) 12-fold, and that the cationic lipid can effectively mediate the virus-cell interaction in the presence of serum and enhance retroviral transduction (pg 130, col.s 1-2). Mizuarai et al suggest that *in vivo* gene transfer using protamine-modified lipid vesicles may be established as a safe and efficient method for gene delivery (pg 131, col. 1, last sentence).

It also would have been obvious to include the method step of hatching the infected/transfected chimeric bird as taught by Ivarie et al because the art has long-recognized the ability, and desirability, to hatch embryos that had been infected with a recombinant retroviral vector for the purpose of testing and mating G0 chimera transgenic birds to establish an avian transgenic line, wherein the exogenous gene can be transmitted to the bird's offspring stably in a Mendelian fashion.

Thus, the invention as a whole is *prima facie* obvious.

12. **Claims 25 and 29-33 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Mizuarai et al (J. Biochem. (January) 129: 125-132, 2001) and Ivarie et al (U.S. Patent No. 6,730,822), as applied to claims 25-29, 34-35 and 37 above, and in further view of Schatten et al (US 2003/0221206), as evidenced by Burns et al (PNAS 90: 8033-8037, 1993; see also Clontech product sheet).

Neither Mizuarai et al nor Ivarie et al teach the administration of at least 10^8 or at least 10^9 virus particles, nor the use of a vector derived from Moloney murine leukemia virus, wherein the virus particle has VSV-G pseudotype. However, at the time the claimed invention, the use of pseudotyped retroviral vectors, such as MoMLV pseudotyped with VSV-G, was routine in the art. Schatten et al disclosed the use of pseudotyped retroviral vectors, such as MoMLV pseudotyped with VSV-G, for the purpose of creating transgenic non-human animals, including birds. Schatten et al do not teach the VSV-G pseudotype to be pseudotype I; however, absent evidence to the contrary, the VSV-G pseudotype of Schatten et al is considered to inherently possess pseudotype I because it is the same VSV-G pseudotype long-used and commercially available in the art (Burns et al; Clontech), as disclosed in the instant specification (pg 26, line 4).

Schatten et al observed that low virus titer and restricted host cell range are major limitations of conventional retrovirus vectors (pg 8, [0082]). Schatten discussed how pseudotyping a retroviral vector with VSV-G could overcome low viral titer and limited host cell range (pg 8, [0083]). Schatten et al contemplated use of various retroviral vectors, including concentrate (10^9-10^{10} cfu/ml) MoMLV (pg 8, [0084]). Schatten et al further discussed the ability of retroviral vectors to deliver heterologous genes to host cells that are susceptible to infection (pg 7, [0079]). The goal of the teachings of Schatten et al appeared to be generation of transgenic non-human animals. See throughout the entire document. Schatten contemplated creation of transgenic birds (pg 1, [0007]).

It would have been obvious to one of ordinary skill in the art to modify the method of Ivarie et al to increase the viral titer as taught by Schatten et al with a reasonable chance of success because the art recognized that infection is a virus titer result-effective variable and the particular known technique of increasing the concentration of a virus titer was recognized as part of the ordinary capabilities of one skilled in the art. One of ordinary skill in the art would have been sufficiently motivated to make such a modification as it was an art-recognized goal to overcome low viral titer and limited host cell range of conventional retroviral vectors as taught by Schatten et al, and particularly since both Schatten et al and Ivarie et al sought to create transgenic birds via retroviral vectors.

It also would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the transgenic bird technology of Ivarie et al by use of an MoMLV vector pseudotyped with VSV-G with a reasonable expectation of success. Although Ivarie et al did not contemplate use of VSV-G pseudotyped MoMLV vectors, Ivarie et al generally embraced use of any retroviral vector. Given that VSV-G pseudotyped MoMLV vectors were available for use and showed improvements over conventional retroviral vectors as per the teachings of Schatten, it would have obvious for Ivarie et al to use a VSV-G pseudotyped MoMLV vector to create transgenic avians because the technique for improving viral transduction using a VSV-G pseudotyped MoMLV vector was part of the ordinary capabilities of a person of ordinary skill in the art, in view of the teaching of the technique for improvement in other situations, and as suggested toward creating transgenic birds.

Thus, the invention as a whole is *prima facie* obvious.

13. **Claims 25 and 36 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Mizuarai et al (J. Biochem. (January) 129: 125-132, 2001), Ivarie et al (U.S. Patent No. 6,730,822) and Schatten et al (US 2003/0221206), as applied to claims 25-35 and 37 above, and in further view of Guild et al (J. Virology 62(10): 3795-3801, 1988).

The prior cited art does not teach the use of the specific chicken β-actin promoter; however, at the time of the invention, Guild et al taught the use of the chicken β-actin promoter in a recombinant Moloney murine leukemia virus vector (pg 3796, col. 2, Construction of internal promoter vectors).

It would have been obvious to one of ordinary skill in the art to substitute the constitutive chicken β-actin/RSV hybrid promoter taught by Mizuarai et al and/or the β-actin promoter taught by Ivarie et al with the chicken β-actin promoter as taught by Guild et al with a reasonable chance of success because the art has long-recognized the ability to use the chicken β-actin promoter with recombinant viral vectors and the simple substitution of one β-actin promoter for a known, equivalent β-actin promoter would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Thus, the invention as a whole is *prima facie* obvious.

14. **Claims 25, 38 and 40 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Mizuarai et al (J. Biochem. (January) 129: 125-132, 2001), Ivarie et al (U.S. Patent No. 6,730,822), Schatten et al (US 2003/0221206) and Guild et al (J. Virology 62(10): 3795-3801, 1988), as applied to claims 25-37 above, and in further view of Rapp et al (US2002/0108132 A1).

The prior cited art does not teach the transgene encodes a chimeric, and hence a fusion protein, antibody. However, at the time of the invention, Rapp et al disclosed a transgenic bird comprising a transgene that encodes an exogenous polypeptide that is an antibody, Rapp et al contemplate transgenic chickens and quails (pg 4, [0041]) transformed with recombinant retroviral expression vectors, including a Moloney murine leukemia virus-derived vector (pg 5, [0052, 0054]; pg 9, [0094-0095]; pg 16, [0158]), wherein said vectors comprise a gene encoding [chimeric] antibodies comprising human immunoglobulin constant domains, single-chain

antibodies, and antibody fragments and/or from birds or mice (pgs 6-7, [0062-0068]; pg 15, [0151]; pg 16, [0161]) operably linked to, for example, constitutive promoters (pg 9, [0090]; pg 16, [0159]).

It would have been obvious to one of ordinary skill in the art to substitute the antibody gene of Ivarie et al with the antibody gene of Rapp et al with a reasonable chance of success because the simple substitution of one known, equivalent element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Thus, the invention as a whole is *prima facie* obvious.

15. **Claims 25 and 39 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Mizuarai et al (J. Biochem. (January) 129: 125-132, 2001), Ivarie et al (U.S. Patent No. 6,730,822), Schatten et al (US 2003/0221206), Guild et al (J. Virology 62(10): 3795-3801, 1988) and Rapp et al (US2002/0108132 A1), as applied to claims 25-38 and 40 above, and in further view of Powers et al (J. Immunol. Methods 251: 123-135, 2001; *of record in IDS), as evidenced by Ono et al (J. Biosci. And Bioeng. 95(3): 231-238, 2003).

The prior cited art does not teach the antibody gene to encode a single-chain Fv-Fc fusion; however, at the time of the invention, Powers et al taught the construction of a single-chain Fc-Fv fusion gene expressed heterologously in yeast.

It would have been obvious to one of ordinary skill in the art to substitute the antibody gene of Ivarie et al or Rapp et al with the antibody gene of Powers et al with a reasonable chance of success because the simple substitution of one known, equivalent element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

An artisan would have been motivated to express an scFc-Fv fusion gene in chickens because Chad et al teach that unlike bacterial expression, animal cell culture and transgenic animal systems have the greatest potential to produce oligosaccharides similar to those contained in human antibodies (Chad et al, pg 189, col.s 1-2, joining sentence). Both human and chicken antibodies can contain oligosaccharides with only the sialic acid *N*-acetylneuraminic acid (NANA), whereas all other species can produce antibodies containing only the sialic acid *N*-glycosylneuraminic acid (NGNA) or a mixture of NGNA and NANA (pg 189, col. 2). The transgenic production of antibodies in egg white has the potential to supply large quantities of

material for clinical trials relatively inexpensively. For example, a flock of 5000 chickens is estimated to produce 125kg of unpurified antibody/year (100 mg antibody/egg and 250 eggs/chicken/year). The commercial cost of chicken eggs (produced under conditions that do not comply with current good manufacturing practice) is currently $0.05/egg. Hence, the cost of generating unpurified material from transgenic chickens is calculated at $0.5/g (Chad et al, pg 191, col. 2, Chickens).

Transgenic production can achieve a lower cost of goods for large-scale manufacturing. Recent advances in the expression of antibodies in transgenic goats, chickens and plants—with respect to productivity, competitive timelines and cost of goods—suggest the need to seriously evaluate these recombinant systems as alternative platforms. Comparing cost of goods analyses between cell culture and the various transgenic production systems, expression in transgenic chickens appears to show great promise when compared with goats and plants (Chad et al, pg 192, col. 2, Conclusions). See also Ono et al for working examples in the art teaching a recombinant retrovirus encoding an scFv-Fc antibody fusion in chicken cells.

Thus, the invention as a whole is *prima facie* obvious.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re*

Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. **Claims 1-6, 10-23, 25-31, 33-41, 44-45, 47, 49-56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting** as being unpatentable over claims 6-14 and 17-22 of copending Application No. 10/569,298 (US 2006/0259997 A1).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The recombinant transgenic bird as claimed is determined to be a product-by-process claim. The recitation of a process limitation in claims 6, 9 and 22 is not viewed as positively limiting the claimed product absent a showing that the process of making recited in claims 11-14 and 17-21 imparts a novel or unexpected property to the claimed product, as it is assumed that equivalent products are obtainable by multiple routes. The burden is placed upon the applicants to establish a patentable distinction between the claimed and referenced products. The method in which the RNAs were produced is immaterial to their patentability.

"Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP §2113.

With respect to the transgenic chimera bird, and transgenic offspring thereof, Iijima et al recite in claims 6-10 and 22 a recombinant bird host/transgenic chimera bird that is indistinguishable from the G0 transgenic chimera bird of the instant application. The claims recite the replication-defective lentiviral vector, wherein the art recognizes that a lentivirus is a type of retrovirus, to comprise a structural gene. The examiner has looked to the specification for a definition of a "structural gene" to better understand the invention.

The specification discloses that the structural gene may be an antibody comprising a human IgG1 constant region or a quail, chicken or mouse IgG, a chimera antibody, or scFv-Fc, wherein said antibodies are abundantly accumulated in the blood, egg white (albumen) or egg yolk (pg 3, [0052], [0053], [0057]; pg 4, [0082]). The structural gene may be operably linked to a constitutive promoter, i.e. chicken beta-actin promoter (pg 3, [0056]).

The claims do not recite the amount of heterologous [antibody] protein present in the blood, albumen or yolk; however, absent evidence to the contrary, such amounts are considered inherent features of the transgenic bird because the structural elements of the vector, e.g. the constitutive promoter operably linked to the gene encoding the heterologous [antibody] protein, necessarily yields the instantly recited amounts in the corresponding tissues.

With respect to the method of producing a transgenic chimera bird, Iijima et al recite in claims 11-14 and 17-21 a method of making a transgenic bird comprising the step of infecting a fertilized egg with a replication-defective lentiviral vector comprising a coat protein containing VSV-G (claim 33 of the instant application), wherein the infection step is performed by microinjection at a period succeeding the blastoderm stage and/or is in the heart or blood vessel formed in the early embryo (claims 25-28 of the instant application), wherein the viral vector has a titer of not lower than $1x10^5$ cfu/ml (claims 29-31), and wherein the bird is a chicken (claim 34).

It would have been obvious to one of ordinary skill in the art that the claimed transgenic bird and claimed method of making said bird of Iijima et al are reasonably embraced by the transgenic bird and the method steps of making the transgenic bird recited in the instant application because the structural elements of the replication-defective retroviral vector and the transgenic bird are species of the instantly recited genus and the method of making said bird are indistinguishable.

17. **Claims 1-59 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting** as being unpatentable over claims 1-30 of copending Application No. 10/585693.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The recombinant transgenic bird as claimed is determined to be a product-by-process claim. The recitation of a process limitation in claims 1-6 and 24 is not viewed as positively limiting the claimed product absent a showing that the process of making recited in claims 1-6 and 7 imparts a novel or unexpected property to the claimed product, as it is assumed that equivalent products are obtainable by multiple routes. The burden is placed upon the applicants to establish a patentable distinction between the claimed and referenced products. The method in which the RNAs were produced is immaterial to their patentability.

"Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP §2113.

Yamashita et al claim a transgenic bird comprising a replication-defective retroviral vector derived from a Moloney murine leukemia virus and having VSV-G pseudoytpe coding for an antibody (pg 18, lines 18-23), wherein said bird is a chicken or quail. The specification discloses that the antibody gene may be an antibody comprising a human IgG1 constant region or a quail, chicken or mouse IgG, a chimera antibody, or scFv-Fc, wherein said antibodies are abundantly accumulated in the blood, egg white (albumen) or egg yolk (pg 7, lines 5-19; pg 8, line 12). The structural gene may be operably linked to a constitutive promoter, i.e. chicken beta-actin promoter (pg 9, lines 8-11).

The claims do not recite the amount of heterologous [antibody] protein present in the blood, albumen or yolk; however, absent evidence to the contrary, such amounts are considered inherent features of the transgenic bird because the structural elements of the vector, e.g. the

constitutive promoter operably linked to the gene encoding the heterologous [antibody] protein, necessarily yields the instantly recited amounts in the corresponding tissues (Yamashita et al, pg 8, lines 19-31).

With respect to the method of producing a transgenic chimera bird, Yamashita et al recite in claims 7-13 a method of making a transgenic bird comprising the step of infecting a fertilized egg with a replication-defective retroviral vector derived from Moloney murine leukemia virus comprising a coat protein containing VSV-G (claims 32-33 of the instant application), wherein said vector comprises a non-retrovirus-derived gene operably linked to a chicken β-actin promoter, wherein said non-retrovirus-derived gene is an antibody, chimeric antibody and/or an scFv-Fc antibody (claims 35-40 of the instant application), wherein the infection step is performed by microinjection at a period succeeding the blastoderm stage (claims 25-28 of the instant application), wherein the viral vector has a titer of not lower than $1x10^7$ cfu/ml (claims 29-31), and wherein the bird is a chicken or quail (claim 34 of the instant application). The method further comprises the step of mating the transgenic bird to another bird so as to create successive generations of transgenic birds (claims 42-43 and 46 of the instant application).

With respect to the method of making a protein, Yamashita et al recite the method step of extracting a desired protein from somatic cells, blood or eggs from a transgenic bird (claims 24 and 48 of the instant application).

With respect to the method of selecting or sorting out a transgenic bird, Yamashita et al recite the method step of collecting sperm and testing sperm samples for the transgene or for confirming the expression of the desired protein in the blood (claims 57-59 of the instant application).

It would have been obvious to one of ordinary skill in the art that the claimed transgenic bird and claimed method of making said bird, the method of producing a protein in a transgenic bird and the method of selecting/sorting out of transgenic birds of Yamashita et al are reasonably embraced by the transgenic bird, the method steps of making the transgenic bird, the method of producing a protein and a method of selecting transgenic birds recited in the instant application because the structural elements of the replication-defective retroviral vector and the transgenic bird are species of the instantly recited genus and the method of making said bird, protein and selection method steps are indistinguishable.

Conclusion

18. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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PRIMARY EXAMINER